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TOPIC HIGHLIGHT

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Inflammatory bowel disease course in Crohn's disease: Is the natural history changing?

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Abstract

Crohn's disease (CD) is a multifactorial potentially debilitating disease. It has a variable disease course, but the majority of patients eventually develop penetrating or stricturing complications leading to repeated surgeries and disability. Studies on the natural history of CD provide invaluable data on its course and clinical predictors, and may help to identify patient subsets based on clinical phenotype. Most data are available from referral centers, however these outcomes may be different from those in population-based cohorts. New data suggest the possibility of a change in the natural history in Crohn's disease, with an increasing percentage of patients diagnosed with inflammatory disease behavior. Hospitalization rates remain high, while surgery rates seem to have decreased in the last decade. In addition, mortality rates still exceed that of the general population. The impact of changes in treatment strategy, including increased, earlier use of immunosuppressives, biological therapy, and patient monitoring on the natural history of the disease are still conflictive. In this review article, the authors summarize the available evidence on the natural history, current trends, and predictive factors for evaluating the disease course of CD.

Key words: Crohn's disease; Natural history; Surgery; Mortality; Disease course; Inflammatory bowel disease

Core tip: Studies on the natural history of Crohn's disease (CD) provide invaluable data on its course and clinical predictors, and may help to identify patient subsets based on clinical phenotype. New data suggest the possibility of a change in the natural history in CD, with an increasing percentage of patients diagnosed with inflammatory disease behavior. Hospitalization rates remain high, while surgery rates seem to decrease in the last decade. Mortality rates still exceed that of the general population. The impact of changes in treatment strategy, including increased, earlier use of immunosuppressives, biological therapy, and patient monitoring on the natural history of the disease are still conflictive.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology. Both genetic and environmental risk factors (*e.g.*, smoking or appendectomy) contribute to its pathogenesis[1]. During

the past two decades, the incidence pattern of inflammatory bowel disease (IBD) has changed significantly[2]. The disease course is reported to be highly variable, but the majority of patients eventually develop penetrating or stricturing complications. Nevertheless, there are still relatively limited data available on the natural history of IBD from population-based studies.

The phenotypic classification of CD based on clinical features plays an important role in patient management, and may help predict the clinical course in CD patients[3]. In 2005, the Montreal revision of the Vienna classification system was introduced[4]. The broad categories for CD classification remained the same [terminal ileum (L1), colon (L2) and ileocolon (L3) and upper gastrointestinal (GI) (L4) as modifier], behavior [non-stricturing non-penetrating (B1), structuring (B2) and penetrating (B3)] with some changes: *e.g.,* upper GI disease and perianal involvement became modifiers classified independently of, or alongside, disease at more distal locations and the later with disease behavior. Current practice guidelines from European Crohn's and Colitis Organisation advocate the use of the Montreal classification in both CD and ulcerative colitis (UC)[5]. Using the Vienna classification system, it has been shown in referral IBD cohorts that a significant change in disease behavior often occurs over time, whereas disease location remains relatively stable[6,7]. It is still uncertain whether this progression is preventable.

Other significant adverse outcomes include need for hospitalization, surgery, and reoperations. Hospitalization and surgery are considered to be markers of disease severity in CD and are associated with high costs[8]. There are relatively limited data available on hospitalization trends, and data interpretation is complicated by local management strategy and reimbursement issues. According to recent population-based studies, major surgery was required in 40% to 50% of CD patients within 10 years of diagnosis in the last 2 to 3 decades, with postoperative recurrence rates as high as 50% at 10 years. However, new data suggest that surgical rates already began to decrease prior to the widespread use of biologicals. The ultimate negative outcome is mortality[9]. CD mortality is still higher than that of the background population and current data do not suggest a change.

Recently, Peyrin-Biroulet *et al*[10] published a systematic review of the natural history of CD in population based-cohorts. According to the authors' conclusions, available data did not suggest a significant change in CD outcome, with approximately half of patients requiring surgery within 10 years of diagnosis. Furthermore, the authors stated that the impact of changing treatment paradigms with the increased use of immunosuppressants and biological agents on the natural history of the disease was poorly understood. In this article, evidence regarding the natural history, the current trends in outcomes and predictive factors for evaluating the disease course in CD, are discussed and summarized.

DISEASE LOCATION, BEHAVIOR AND OVERALL DISEASE ACTIVITY: CHANGING PATTERNS OR DIFFERENCES DUE TO DIAGNOSTIC TOOLS, AGE AT ONSET, GEOGRAPHIC REGION AND HOSPITAL SETTING?

In CD, disease location at diagnosis is relatively homogeneous and stable, with the exception of the reported variance in the frequency of upper gastrointestinal location, especially when comparing pediatric- and adult-onset populations. In addition, according to some studies, the proportion of isolated colonic disease seems to have increased in the last decade. In the recent study by the IBSEN group[11], 27% of patients had L1 disease, 48% L2, 23% L3, and 2% L4 disease at presentation. Somewhat lower rates of isolated colonic disease were reported from Denmark (L2: 30%, 43%, and 37%, in 1962-1987, 1991-1993 and 2003-2004, respectively)[12]. Similar data were recently reported from Eastern Europe (L1: 20%; L2: 35%, L3: 44%, and L4: 2.4%) in 2002-2006[13]. Somewhat lower frequency of ileocolonic disease was reported from the Mayo Clinic[14]. Disease extent was ileal in 45.1%, colonic in 32.0%, and ileocolonic in 18.6%.

Finally, two very recent, multinational, population-based cohorts have come to similar conclusions. In the EpiCom study[15], the distribution was not significantly different in centers from Western and Eastern Europe (L1: 35% *vs* 43%, L2: 31% *vs* 24%, L3: 27% and 32%, isolated L4: 8% and 2%, total L4 involvement: 24% *vs* 17%). The frequency of total upper gastrointestinal involvement was higher compared to previous reports. Another study was published from eight countries across Asia and Australia[16]. Interestingly, disease location was very similar in the Asian countries and Australia (L1: 31%, L2: 24%, L3: 45%, and L4: 5%). The highest variability is reported in the rate of upper gastrointestinal involvement. This may be at least partly associated with diagnostic procedures (*e.g.*, completeness of bowel investigation), but differences in the definitions and interpretation of minute upper gastrointestinal lesions. As an example, in the recent EpiCom study, only 10%-34% of adult onset patients underwent a gastroscopy, while a full colonoscopy was performed in 93%-96%. Additional small bowel imaging (capsule endoscopy, magnetic resonance imaging, or computed tomography) was performed approximately 60% of CD patients. Of note, location seems to be relatively stable with only 10%-15% change after approximately 10 years' follow-up[7,17,18].

Up to one-third of patients present with complicated disease phenotype at diagnosis. In the IBSEN cohort, 36%, 49%, and 53% of patients presented with stricturing or penetrating disease at diagnosis or developed such complications within 5 or 10 years. However, some recent studies also reported a change in the initial disease behavior over time. In the Veszprem cohort, patients

diagnosed from 1999 to 2008 presented more frequently with inflammatory disease behavior compared to the previous cohort (65% *vs* 50%)[18]. Similarly, the probability of progression to complicated disease behavior was associated with the calendar year of diagnosis, but not with age at onset; after five and seven years 15.1% and 21.8% of patients diagnosed after 1998 progressed to complicated disease, while 27.4% and 33.3% of patients diagnosed between 1977 and 1998 showed such a progression. Other factors identified were disease location, perianal disease and smoking.

Recently, authors from New Zealand[17] published a population-based cohort study, showing that > 70% of CD patients had inflammatory disease at diagnosis, while only 23% and 40% of patients with initial inflammatory disease progressed to complicated disease phenotypes after five and ten years of follow-up, respectively. The median follow-up for CD patients was, however, only 6.5 years. In a study from the Mayo Clinic, 81.4% had non-stricturing, non-penetrating disease, 4.6% had stricturing disease, and 14.0% had penetrating disease at diagnosis[14]. Similarly, only 22% of patients had fistulizing complications in the Manitoba CD cohort[19]. The cumulative risk of developing either complication in the Mayo cohort was 18.6% at 90 d, 22.0% at 1 year, 33.7% at 5 years, and 50.8% at 20 years after diagnosis. Similarly, B1 behavior was observed in 68% and 75% of patients in Western and Eastern Europe, respectively in the EpiCom study[15] with 10% of all patients presenting with perianal involvement. The rate of inflammatory disease behavior was even higher in Australian patients in the ACCESS study[16] (Australia: 88% *vs* Asian countries: 66%), with similar perianal involvement (12% and 18%). Another remarkable finding of this study was that UC incidence increased parallel with age. Nonetheless, some of these changes may result from bias due to diagnostic delay, differences in the diagnostic tools and completeness of bowel examination in the different time periods.

In contrast, in the landmark study by Cosnes *et al*[6], up to 70% of CD patients developed either penetrating or stricturing disease within 10 years of diagnosis in a referral CD cohort. Similar results were published in a Belgian referral cohort[17]. During 10 years' follow-up, 45.9% of patients had a change in disease behavior from non-stricturing, non-penetrating disease to either stricturing (27.1%) or penetrating (29.4%) phenotypes. In contrast, disease location remained relatively stable during follow-up, with only 15.9% of patients exhibiting a change in disease location within 10 years. The rate of perianal complication varies between 10%-20% at presentation. Of note, these were referral center cohorts and as highlighted earlier, trends were to some extent different in the population-based setting.

According to the available literature, pediatric-onset CD runs a more aggressive course, with more extensive disease location, more upper GI involvement, more active disease, growth failure, and need for more aggressive medical therapy in predominantly referral-center studies[20-22]. While data on overall disease course so far have lacked consensus, pediatric disease behavior seems to parallel that of adults[23]. A Scottish study simultaneously compared disease behavior and location in pediatric and adult onset IBD patients[24]. In childhood-onset patients a clear difference in disease location at onset and after five years exists; with less ileum- and colon-only location but more ileocolonic and upper gastrointestinal involvement among pediatric-onset patients ($P < 0.001$ for each). In addition, disease behavior after five years did not differ between the two groups. Similar trends were recently reported from the Eurokids registry with a larger proportion of pediatric-onset patients presenting with extensive disease (L1: 16%, L2: 27%, L3: 53%, and L4: 54%)[22]. Finally, according to French data, pediatric-onset CD was characterized by frequent occurrence of a severe phenotype during follow-up, with extensive location, complicated disease, and frequent need for immunosuppressives[25].

Additionally, according to the findings by Pigneur *et al*[21], patients with childhood-onset CD often have more severe disease, increased frequency of active periods, and increased need for immunosuppressants. In contrast, the cumulative risks of stricturing and penetrating complications and need for surgery were not different between childhood-onset and adult-onset patients. Similar findings were reported recently from a population-based study including both pediatric and adult onset cohorts from Hungary[18] and another from Canada[26]. Interestingly, in the most recent publication from the EPIMAD registry[27], patients with pediatric-onset disease had roughly similar disease behavior at diagnosis compared with patients with an age at onset between 17-39 years, 40-59 year or > 60-years (B1: 72%, 66%, 69% and 78%). In this paper, pediatric-onset patients presented more frequently with ileocolonic disease, while elderly-onset CD patients (> 60 years at diagnosis), isolated colonic disease. In addition, complicated disease developed significantly more frequently in the pediatric-onset patients compared to patients with an elderly onset (50% *vs* 30% at maximal follow-up). The disease course in elderly-onset patients was altogether milder[28]. Similar findings were reported also form Hungary[29].

Few data are available regarding relapse rates and overall disease course in IBD. Most data were published from the Nordic countries. In one early publication, long-term disease course was reported in 185 CD patients followed-up regularly between 1960-1978 in Copenhagen[30]. About 45% of patients were clinically asymptomatic for all observation years. The disease activity was low in approximately 30% of patients and moderate-to-high in approximately 25%. Continuous disease activity was observed in about 20% of patients and intermittent symptoms were reported in 35% of those with active disease in a given year. However, the cumulative relapse rate after five years reached 93.1%. Similar disease course was reported in a follow-up cohort from the same region in 1991-1993[12].

Somewhat different rates were published in the EC-

IBD study[31]. All-type first cumulative recurrence rates were 34%, 69.2%, and 77.5% after 1, 5, and 10 years of follow-up, respectively, in 358 CD patients, with similar second and third all-type relapse rates (40.2%, 76.9% and 82.6% *vs* 45.9 and 76.4% after 1, 5, and 10 years). Upper gastrointestinal location and therapy with 5-aminosalicylic acid therapy were associated with increased risk of relapse. Interestingly, relapse rates were associated with the geographic region. Higher relapse rates were reported from Copenhagen, while lower rates were observed in Greece, Italy, and Norway. Similar to earlier reports, high cumulative relapse rates (53%, 85% and 90% after 1, 5, and 10 years, respectively) were reported recently from the IBSEN group[11]. This was associated with early need for steroids but not with disease phenotype or smoking habits. In contrast, approximately 44% of patients were in clinical remission during the second five-year period and 43% experienced a decrease in disease severity (according to predefined disease patterns) during the follow-up period. In contrast, 3% of patients experienced an increase in severity, 19% experienced chronic continuous symptoms, and 32% experienced a relapsing course.

HOSPITALIZATION: IS THIS AN OBJECTIVE MEASURE?

Although hospitalization is an important outcome measure, it is subject to inconsistency, as it is influenced by multiple factors other than disease severity, such as the need for diagnostic workup, health insurance reimbursement policies and ethnic differences. In addition, the threshold for hospitalization varies between specialized centers, community hospitals, and private practice. In addition, a restructuring of costs is currently seen, as highlighted in a short-term study from The Netherlands[32]. In this study, tumor necrosis factor inhibitors (anti-TNFs) accounted for as much as two-thirds of the direct costs in CD and one-third in UC (with a three-month total cost of 1626€ in CD and 595€ in UC). Future studies are needed to investigate if tight control and aggressive therapy based on early patient profile stratification leads to superior long-term outcomes. A cost-benefit analysis is also required to justify the cost burden of these medications.

Relatively few data are available regarding hospitalization rates in patients with CD. Several decades ago, a significant proportion of diagnostics were performed on an inpatient basis, leading to fairly high initial hospitalization rates as reported in Scandinavia. For example, in Copenhagen the hospitalization rate in the year of diagnosis 83% in CD patients from 1962 to 1987. In addition, approximately 20% of patients were admitted yearly over the next five years[33]. Data from the 1990s is available from a pan-European prospective follow-up study[34]. This study confirmed that hospitalization rates declined significantly from the second year after diagnosis. The cumulative risk of overall hospitalization was also lower compared to the previous year (52.7% at 10 years from diagnosis) but with considerable differences between countries. Rates were highest in Denmark, Ireland, Portugal while low rates were observed in Norway, Greece, and Italy.

Likewise, high hospitalization rates were reported in a population-based study from Canada[35]. In 1994-2001, approximately 25% of subjects with Crohn's disease were admitted annually. The annual hospitalization rate declined from 29.2 to 26.9 per 100000 over the seven years of the study. The readmission rate was 39.4%, with almost half of the hospitalizations occurring for surgery. In a more recent population-based study from the same region[36] the authors reported stable hospitalization rates in CD patients diagnosed between 1988 and 2008, with the highest hospitalization rates within the first year of diagnosis (approximately 1.3 admissions per person-year). Similar to previous studies, hospitalization rates declined after the first year by about half with a stable rate over the next 5 years.

A meta-analysis of hospitalization rates in IBD was published from nine European countries based on the data of the national statistic offices in 2009[37]. Hospitalization rates varied significantly among countries, ranging between 1.2 and 4.3 discharges per 10000 for CD. The highest rates were found in Denmark (4.33) and Scotland (4.15), with the lowest in Spain (1.20), Switzerland (1.31) and the Netherlands (1.46), a trend partly unrelated to disease prevalence. Numbers were similar for UC and CD in the given country with a specific age-distribution pattern (CD: High peak in 20-30 year old patients and small peak in the elderly; UC: Opposite trend).

Finally, multiple studies investigating US national databases reported an increase in CD related hospitalization rates. However, it is difficult to determine if this rise is associated with disease prevalence, severity or both. According to the National Hospital Discharge Survey database, CD-related hospitalization rates increased significantly from 9.3 to 17.1 per 100000 from 1990 to 2003[38]. In particular, hospitalization rates in the 45-64 year-old and > 65 year-old groups rose significantly, while rates in younger patients remained essentially unchanged[39]. Similar trends were reported from the Nationwide Inpatient Sample[40]. Hospitalization rates increased 4.3% annually between 1998 and 2004. In contrast, data from Kaiser-Permanente suggested a decrease in CD-related hospitalization rates by about one-third between 1998 and 2005[41] parallel with an increased use of IBD related drugs (including a fivefold increase in anti-TNF use) and a shift in gastroenterology-related visits from the gastroenterology division to primary care.

In conclusion, although hospitalization patterns and causes may have changed, rates are still high, with approximately 50% of CD patients requiring hospitalization within 10 years of diagnosis. Actual rates may vary significantly among age groups, time periods, reimbursement settings, and among countries. Findings must be interpreted with attention given to the context of disease prevalence, treatment strategy, and health care access.

SURGERY IN CROHN'S DISEASE: RATES, TRENDS AND CAUSES

Surgery is one of the most objective outcome measures, since it is only performed if clinically indicated. Almost decade ago, partly based upon historical data, the probability of surgery was reported between 3% and 96% within 15 years of diagnosis[42], with clinical relapse and reoperation rates of 50%-60% and 28%-45%, respectively, during the subsequent 15 years. Surgical resection rates over time vary widely among published studies, ranging between 25% and 61% in the first five years. Early studies reported extraordinarily high surgical rates, as high as 30%, 50%, and 60% at 5, 10, and 15 years, respectively, in the population-based Stockholm County cohort from 1955-1974[43]. Surgical rates did not seem to change according to an update from the same cohort[44]. Even higher rates were reported some years later in a population-based cohort from Denmark[45], with up to 35% of CD patients requiring surgery in first year after diagnosis. The cumulative surgery rate was 61% and 82% after 10 and 20 years.

Lower surgery rates were reported in the pre-biologic IBSEN cohort[11]. In patients diagnosed between 1990-1994, surgery rates of 14%, 27%, and 38% at 1, 5, and 10 years were observed. Similar surgery rates were reported from the multinational European EC-IBD cohort diagnosed in the same time period with a cumulative surgery rate of 37.2% after 10 years and reoperation rates of 2.2%, 18.5%, and 35.9% at 1, 5, and 10 years, respectively[31]. A geographic variability was reported. Patients from northern European centers, especially Copenhagen, had higher surgical need due partly to differences in disease phenotype. Interestingly, cumulative surgery rates were comparable from a recent publication from a referral center in South Korea[46], which reported data from 1991 to 2007, which showed cumulative probability of surgery of 15.5%, 25.0%, and 32.8%, at 1, 5, and 10 years after diagnosis, respectively. Surgery rates in referral center may not be directly comparable with that reported from population-based studies, however. Geographic variability is also evident in Asia, as surgery rates were much higher in a Japanese referral center cohort[47], reaching as high as 37.6%, 60.4%, and 74.2% at 5, 10, and 15 years. This is comparable to historical studies from Europe in the 1960s and may represent a distinct patient management strategy.

An association with disease phenotype was reported in multiple studies. Terminal ileal location, stricturing or penetrating disease, and younger age at diagnosis (< 40 years) were identified as risk factors for surgery. Recent data from Canada, Denmark, the United Kingdom, and Hungary, however, suggest that surgical rates were falling (Table 1) prior to the advent of biologic therapy, as summarized by the IOIBD Epidemiology Task Force report[8]. This trend is best highlighted by a Danish study[12]. The rate of early surgery (within one year of diagnosis) fell from 35% to 12% between 1962 and 2004 Risk has continued to decline, parallel with increased use of immunosuppressives and biologicals, although causality was not established[48]. Similar trends were reported in a population-based CD cohort from Manitoba, Canada[37,38]. Surgery rates at one and five years decreased from 13% and 22% in patients diagnosed between 1996 and 2000 to 10% and 18% for those diagnosed between 2001 and 2008 (HR = 0.79; 95%CI: 0.65-0.97). Reoperation rates were unaffected by the era of diagnosis. In contrast, high operation rates were reported from the Mayo Clinic[10] in patients diagnosed between 1940 and 2001 with a cumulative risk for surgery 24%, 49%, and 64% at 1, 10 and 30 years from diagnosis, respectively. In an update of the same cohort, presented in an abstract form, surgery rates did not seem to decline in patients diagnosed between 1970 and 2004 with 38%, 48%, and 61% of patients being operated on at 5, 10, and 30 years.

An association was also suggested with a change in disease management including tight follow-up and early immunomodulator therapy, however data are partly conflictive. In a previous referral center study from France, the need for intestinal surgery did not decrease despite increased use of immunosuppressants[49]. However, in this study immunosuppressives were almost exclusively started after surgery. In contrast, recent population-based reports from Wales and Hungary[50,51] reported that early azathioprine (AZA) use may be associated with reduced

Table 1 Surgery trends for Crohn's disease in population based cohorts by years from initial diagnosis

Geographic region and time period of investigation	Time from diagnosis		
	1 yr	5 yr	10 yr
North America/Asia			
Olmsted County, MN, United States[38]			
1970-2009		38%	48%
Manitoba, Canada[2]			
1988-2008	13%	24%	32%
2001-2008	10%	18%	
South Korea[39][1]			
1991-2007	15%	25%	33%
Europe			
Sweden[21]			
1955-1974		30%	50%
Denmark[25-37]			
1960-1978	35%		61%
2003-2005	12%		
Denmark[51]			
1979-1986		44.70%	
2003-2011		19.60%	
Norway[28]			
1990-1994	14%	27%	38%
Wales, United Kingdom[32]			
1986-1991	32%	59%	
1992-1997	25%	37%	
1998-2003	19%	25%	
Veszprem Province, Hungary[32,33]			
1977-2008	15%	31%	52%
2002-2006	10%	21%	
EC-IBD[29]			
1991-2003			40%

[1]Referral cohort.

frequency of resective surgery. In the study from Wales, surgery rates decreased from 59% to 25% at five years after diagnosis between 1986 and 2003. A similar five-year surgery rate (21.3%) was reported in the latter study in patients diagnosed between 2002 and 2006[13]. In addition, a French study reported an association between the duration of anti-TNF and AZA therapy and risk for surgery[52]. Of course, long treatment duration allows responders to the above therapies to be identified.

While data are mixed and there exists geographic variation, recent data suggest a multifactorial trend for decreasing surgery. Disease behavior at diagnosis as reported in the most recent studies is more often inflammatory compared to earlier CD cohorts[15,16,18]. In addition, diagnostic tools and follow-up strategy has changed significantly in the last decade, parallel with the earlier and more widespread use of immunosuppressives, as reported in a recent publication from Canada[37]. In this study, authors reported an association between early gastroenterologist care and lower risk of surgery parallel with an increased early use of immunosuppressives. However, exposure to immunosuppressives is still relatively limited in the population-based studies and reoperation rates are essentially unchanged.

However, results from two recent prospective randomized clinical trials cast some doubt on the efficacy of early thiopurine therapy. In the first paper, the GETAID group[53] reported that early aggressive therapy with AZA (2.5 mg/kg) within 6 mo of diagnosis was no more effective than conventional management in increasing time of clinical remission as assessed by trimesters for 36 mo. However, 61% of the patients in the "conventional" group required AZA within a median of 11 mo of diagnosis, which cannot be interpreted as a conservative approach. Therefore, a more accurate interpretation is that authors compared early aggressive strategy with an early-accelerated strategy, and still the need for perianal surgery was lower (4% *vs* 18%, $P = 0.036$). Another study, AZTEC, from the Spanish IBD group[54], appears promising in design; early CD patients (< 8 wk of diagnosis), after entering remission, patients were randomized to receive AZA or placebo. The endpoint was steroid-free remission at week 76. Unfortunately, the trial was stopped for futility; therefore the power of the study is somewhat questionable.

A more precise interpretation of the results reveals difficulties. First, diagnosis can still change in approximately 10% to 15% of CD patients during follow-up, as suggested the IBSEN group. Thus, 8 wk from the first specialists visit and diagnosis may introduce some unintentional bias with regards to the above. Second, we must assume that 30% of patients entered remission without steroid therapy, since under standard steroid taper schedules patients treated with steroids at diagnosis should still have received steroids at 8 wk. In addition, approximately one fourth of patients entered the trial without clinical remission. In contrast, median C-reactive protein (CRP) was low (CRP at diagnosis was not given). Of note, 92% of patients had inflammatory disease, extensive location was observed in only one-third of patients, and patients with fistulizing (internal penetrating or perianal fistula) or stenosis were excluded. Thus we propose an alternative interpretation of the findings: mild phenotype patients at diagnosis do not necessarily benefit from early AZA therapy in the short term. However, this trial does not provide data on the efficacy of early AZA therapy in patients with complicated disease phenotype at diagnosis, nor whether AZA has the potential to change the natural history of the disease. In addition, the definition of clinical relapse was based simply on CD activity index (CDAI) and this does not adequately define steroid-free status, since under this definition most patients would have a relapse as defined by a CDAI elevation before they would need steroids. This is indeed a very soft endpoint. Interestingly, with a modified definition of relapse (CDAI > 220) AZA patients had a significant clinical benefit, even bearing in mind the limitations of CDAI. From this trial, it should be clear that the use of CDAI is insufficient as the only definition of relapse. Other objective parameters are needed, such as a change in CDAI > 100 from baseline, a need for a change in the medical therapy, or the development of complications. Development of complicated disease or need for surgery would be the optimal outcome measures to study the natural history of the disease.

Of note, surgery should not always be regarded as a negative outcome, and it has an important place in the management of CD patients. Early surgery has been shown to prolong clinical remission (HR = 0.57; 95%CI: 0.35-0.92)[55]. In addition, CD patients with limited complicated terminal ileitis diagnosed at surgery were reported to have low reoperation rates, and needed less steroids and immunosuppressants during follow-up than those not diagnosed intra-operatively[56]. The same was proven for early terminal ileum resection in a population-based Hungarian cohort[57]. In these patients, surgery is part of a proactive treatment strategy and possibly represents an alternative to medical therapy. On the other hand, surgery during the first 6-10 mo of diagnosis is clearly linked to unavoidable complications already present at diagnosis. Unfortunately, this is more representative of the initial cohort characteristics and should not be interpreted as a real outcome measure. Thus, if we would like to study the association between management and treatment strategy most probably these patients should be excluded from the analysis. Finally, the above surgery rates and trends were reported from the pre-biologic era in cohorts with no or only minimal or anti-TNF/biological exposure. Whether biological therapy directly influences long-term surgery trends outside of clinical trials remains unclear.

MORTALITY

In a meta-analysis from 2010, mortality in CD was increased with a pooled standardised mortality (SMR) of 1.39 (95%CI: 1.30-1.49)[58]. The meta-analysis included

Table 2 Key issues on the natural history of Crohn's disease

-The distribution of location in Crohn's disease (CD) has not changed significantly in the recent decade, but differs according to age at onset
-Recent data indicate that there are an increasing proportion of Crohn's disease patients are diagnosed with an inflammatory disease behavior. The progression to complicated disease phenotype is decreased
-There is evidence from population-based studies that the surgery rates have recently declined in Crohn's disease
-Data suggest that the decline in the surgical rates is partly associated with early use of thiopurines. However, the relative importance of changes in treatment strategy and patient monitoring on the natural history remain conflictive
-Overall mortality rates in CD have been higher than that in the background population, and there is only little evidence that these have changed in the last decade. In addition, an increased mortality from gastrointestinal causes is constantly reported
-Further data are needed to assess whether tight, and objective patient monitoring (including clinical, laboratory, endoscopy and imaging) or early administration of biological would lead to superior outcomes
-Cost-effectivity of the new treatment and monitoring strategies has to be established

nine population-based studies of which eight were European (including an EC-IBD study). Causes identified were cancer, COPD, gastrointestinal disease, and genitourinary disease. A recent nationwide study from Denmark confirmed a 50% increased mortality in CD, and concluded that mortality in CD did not decrease over time, despite a change in patient management[59]. Similar results were published some years earlier in another meta-analysis[60], which included referral center data. In subgroup analyses, the SMR ratio was increased in hospitals (SMR = 1.73; 95%CI: 1.45-2.47), referral centers (SMR = 2.06; 95%CI: 1.63-2.60), and population-based studies (SMR = 1.48; 95%CI: 1.28-1.70).

In contrast, the authors of two very recent population-based studies failed to confirm an increase in the overall CD mortality. In a study from Finland, mortality was not increased in 1915 adult IBD patients in 1986-2007. Mortality was increased from diseases of the digestive system, but there was a reduced mortality from mental and alcohol-related behavioral disorders compared to the general Finnish population[61]. Another recent population-based study from South-Limburg, in the Netherlands did not find increased overall mortality in CD between 1991 and 2003 (SMR = 1.1; 95%CI: 0.7-1.6), despite increased mortality from gastrointestinal causes (SMR = 7.5; 95%CI: 2.8-16.4) in this patient group[62]. This concurs with previous reports from the Mayo Clinic, where authors did not find increased mortality in 314 patients between 1940-2001 (SMR = 1.2; 95%CI: 0.9-1.6)[63]. In addition, an increased risk of dying from non-malignant gastrointestinal causes (SMR = 6.4; 95%CI: 3.2-11.5), gastrointestinal malignancies (SMR = 4.7; 95%CI: 1.7-10.2), and COPD (SMR = 3.5; 95%CI: 1.3-7.5)) was also observed. In contrast, another study from Kaiser Permanente reported increased mortality in CD patients between 1996 and 2003 (SMR = 1.4; 95%CI: 1.2-1.6)[64]. In conclusion, there is insufficient evidence to support the hypothesis that overall CD mortality trends has changed, it is slightly increased together with a consistently increased mortality having been reported form gastrointestinal causes.

SUMMARY AND CONCLUSION: IS THE NATURAL HISTORY OF CD CHANGING?

Studies on the natural history of CD provide invaluable data on the disease course as well as clinical predictors, and may help identify patient subsets based on clinical phenotype. Most data are available from referral centers, however outcomes are different from data reported from population-based cohorts, so that results are not directly comparable.

New data suggest a possible change in the natural history of Crohn's disease (Table 2), with increasing numbers of patients diagnosed with inflammatory disease behavior, likely, one would hope, due to new diagnostic techniques and tools. Hospitalization rates remain high, yet hospitalization is a relatively soft endpoint, and actual rates may vary significantly according to age group, reimbursement setting, and countries. Findings must be interpreted with attention to disease prevalence, treatment strategy, and health care access. In contrast, surgery rates seem to have decreased in the last decade, yet it is difficult to identify the drivers of this change. A combination of the greater proportion of patients with uncomplicated disease behavior, changes in patient monitoring, different therapeutic strategies, and altered attitude towards surgery may be at least partly responsible. Finally, mortality rate in CD still exceeds that in the general population and there is only little evidence that this has changed.

The impact of changing treatment strategy on the above trends, including increased, earlier use of immunosuppressives and biologicals, and changed systems for patient monitoring on the natural history is not entirely clear. Unfortunately, data from randomized clinical trials are of limited value in studying the natural history of the disease. This is partly because follow-up is limited in duration and open-label extensions include the same confounders as population-based cohorts. In addition, the patient populations do not reflect the patients from everyday clinical practice, as highlighted by a recent paper from the United States[65]. Therefore, a direct extrapolation of the findings to the clinic is often difficult.

In conclusion, for clinical practice, it is important to use available results from the published literature. We must identify markers of progressive as well as mild disease, since an early patient stratification enables clinicians to select the most appropriate therapy for a given patient. Further data are needed to investigate whether tight, objective patient monitoring and early administration of biological agents lead to superior outcomes. Some clinical trials are underway (CALM, REACT) and results will be available soon. However, the cost-effectiveness of the new treatment and monitoring strategies also must be established in the near future. In addition, it will be extremely important to follow-up the recent multinational,

multicenter, population-based patient cohorts (EpiCom and ACCESS), since accurate long-term data on harder endpoints such as complications, surgery, and ultimately mortality in the biological era is urgently awaited, and can be obtained only in this setting. The key factor is the appropriate adjustment for confounders.

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